

From the Department of Public Health Sciences | Global Health
Karolinska Institutet, Stockholm, Sweden

Retention during the first year of HIV care and the effect of an interactive text-messaging service on patient engagement in care

Mia Liisa van der Kop



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RETENTION DURING THE FIRST YEAR OF HIV CARE AND THE EFFECT OF AN INTERACTIVE TEXT-MESSAGING SERVICE ON PATIENT ENGAGEMENT IN CARE

THESIS FOR DOCTORAL DEGREE (Ph.D.)

By

Mia Liisa van der Kop

Principal Supervisor:

Professor Anna Mia Ekström
Karolinska Institutet
Department of Public Health Sciences
Global Health/IHCAR
Sweden

Co-supervisor(s):

Dr. Richard Todd Lester
University of British Columbia
Department of Medicine
Infectious Diseases
Canada

Dr. Patricia Opondo Awiti
Karolinska Institutet
Department of Public Health Sciences
Global Health/IHCAR
Sweden

Dr. David I Ojaka
University of Eldoret
Kenya

Opponent:

Dr. Michael Law
University of British Columbia
School of Population and Public Health
Health Services and Policy
Canada

Examination Board:

Professor Lucie LaFlamme
Karolinska Institutet
Department of Public Health Sciences
Global Health/IHCAR
Sweden

Dr. LaRon Nelson
Yale University
Department of Medicine
Global Health and Equity
USA

Dr. Jerry Spiegel
University of British Columbia
School of Population and Public Health
Health in Populations
Canada

Dedicated to people living with HIV in Kenya, the staff at the Kibera Community and Baba Dogo Health Centres, and African researchers working hard to improve the health of people living in low-income settings.

ABSTRACT

Background: Retention in HIV care is critical to ensure timely treatment initiation, viral suppression, reduced transmission, and to prevent AIDS-related deaths. Retention in care is low and falls short of the level needed to meet the UNAIDS 90-90-90 targets. There are few interventions designed to improve retention in HIV care and quantifying retention in care has been mostly limited to quantifying 'retention in clinic'. 'Retention in clinic' accounts for those who return to the clinic at which they were originally enrolled but does not consider informal or formal transfers, which are common in sub-Saharan Africa. The overall aim of this thesis was to quantify retention in HIV care and to investigate whether the WelTel text-messaging intervention, previously found to improve antiretroviral therapy adherence, improved retention during the first year of HIV care. Ancillary studies using baseline data were also conducted as part of this thesis.

Methods: Between April 2013 and June 2015, adults testing HIV-positive were recruited at two clinics in informal settlements in Nairobi, Kenya. Individuals ineligible for the trial because they did not meet phone-related trial eligibility criteria were invited to participate in a supplementary cohort study. In the trial, intervention arm participants received a weekly text-message and were asked to respond within 48 hours. The primary outcome was retention in care at 12-months (clinic attendance 10-14 months after the first visit). Participants who did not attend this 12-month appointment were traced and those confirmed active in care elsewhere were considered retained. All participants, both in the trial and cohort study, were followed for up to 14 months to quantify retention in care at one year. Baseline data for the entire study population were used to conduct additional studies on advanced HIV at presentation to care and a gender analysis of health-related quality of life at the time of a positive HIV test.

Results: Of 700 individuals recruited for the trial, 349 were allocated to the intervention and 351 to the control arm. At 12 months, 79.4% (n=277/349) of intervention arm participants were retained in care compared to 81.2% (n=285/351) of control arm participants (risk ratio 0.98, 95% confidence interval [CI] 0.91 – 1.05). In the larger cohort study (n=775), 62.7% (95% CI 59.2% - 66.1%) of participants returned to the clinic for their 12-month appointment (retained in clinic) and 609 (78.6%, 95% CI 75.7% - 81.5%) were retained in care at any HIV clinic. In the first ancillary study, 248/753 (32.9%) participants presented to care with advanced HIV, 59.0% (146/248) of whom had been previously diagnosed with HIV. In the second ancillary study, the mean physical composite score was statistically significantly higher in women than men at the time of an HIV diagnosis (adjusted mean difference [AMD] 2.49, 95% CI 0.54 - 4.44). There was no significant difference between the genders in mental composite scores (AMD -0.99, 95% CI -2.71 - 0.73).

Conclusions: Presentation to care with advanced HIV was primarily due to delayed diagnosis, rather than delayed linkage to care after diagnosis. Variation by clinic suggests that outreach and other community-based efforts may drive earlier testing and linkage to care. After receiving a positive HIV test, men and women had similar mental health scores, while women reported greater physical health. The weekly WelTel text-

messaging service did not improve retention in early HIV care in this setting. Both in the trial and cohort study, retention in clinic substantially underestimated retention in care one year after presenting to care. While the proportion of patients retained in care was greater than expected, interventions to improve retention in care are needed to meet global targets to end the AIDS epidemic.

Keywords: HIV, mHealth, retention in care, Kenya, informal settlement, randomized controlled trial, health-related quality of life, advanced HIV

LIST OF SCIENTIFIC PAPERS

- I. **Mia Liisa van der Kop**, Lehana Thabane, Patricia Opondo Awiti, Samuel Muhula, Lennie Bazira Kyomuhangi, Richard Todd Lester, Anna Mia Ekström.
Advanced HIV disease at presentation to care in Nairobi, Kenya: late diagnosis or delayed linkage to care?—a cross-sectional study.
BMC Infect Dis. 2016;16:169.
- II. **Mia L van der Kop**, Samuel Muhula, Anik Patel, Lehana Thabane, Patricia Awiti, Lennie Kyomuhangi, Bonface Abunah, Patrick I Nagide, Kirsten Smillie, David I. Ojaka, Joshua Kimani, Anna Mia Ekström, Richard T Lester.
Gender differences in health-related quality of life at the time of a positive HIV test—a cross-sectional study in a resource-poor, high prevalence setting in Nairobi, Kenya.
AIDS Care. 2018;30(4):493-499.
- III. **Mia L van der Kop**, Patrick I Nagide, Lehana Thabane, Lawrence Gelmon, Lennie B Kyomuhangi, Bonface Abunah, Anna Mia Ekström, Richard T Lester.
Retention in clinic versus retention in care during the first year of HIV care in Nairobi, Kenya: a prospective cohort study.
J Int AIDS Soc. 2018;21(11):e25196.
- IV. **Mia Liisa van der Kop**, Samuel Muhula, Patrick I Nagide, Lehana Thabane, Lawrence Gelmon, Patricia Opondo Awiti, Bonface Abunah, Lennie Bazira Kyomuhangi, Matthew A Budd, Carlo Marra, Anik Patel, Sarah Karanja, David I Ojaka, Edward J Mills, Anna Mia Ekström, Richard T Lester.
Effect of an interactive text-messaging service on patient retention during the first year of HIV care in Kenya (WelTel Retain): an open-label, randomised parallel-group study.
Lancet Public Health. 2018;3(3):e143-e152.

LIST OF RELATED PUBLICATIONS

- I. **Mia L van der Kop**, David I Ojakaa, Anik Patel, Lehana Thabane, Koki Kinagwi, Anna Mia Ekström, Kirsten Smillie, Sarah Karanja, Patricia Awiti, Edward Mills, Carlo Marra, Lennie Bazira Kyomuhangi, Richard T Lester.
The effect of weekly short message service communication on patient retention in care in the first year after HIV diagnosis: study protocol for a randomised controlled trial (WelTel Retain).
BMJ Open. 2013;3:e003155.
- II. **Mia L van der Kop**, Samuel Muhula, Anna Mia Ekström, Kate Jongbloed, Kirsten Smillie, Lawrence Gelmon, David I Ojakaa, Richard T Lester, Patricia O Awiti.
Participation in a mobile health intervention trial to improve retention in HIV care: does gender matter?
J Telemed Telecare. 2016;23(2):314-320.

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LIST OF ABBREVIATIONS

AIDS	Acquired Immune Deficiency Syndrome
AMD	Adjusted Mean Difference
AOR	Adjusted Odds Ratio
ARR	Adjusted Risk Ratio
ART	Antiretroviral Therapy
CBO	Community-Based Organization
CDC	Centers for Disease Control and Prevention
CI	Confidence Interval
DSMB	Data Safety and Monitoring Board
FBO	Faith-Based Organization
HARKing	Hypothesizing After the Results are Known
HIV	Human Immunodeficiency Virus
HRQoL	Health-Related Quality of Life
IQR	Interquartile Range
MCS	Mental Composite Score
MD	Mean Difference
mHealth	Mobile Health
NGO	Non-Governmental Organization
OR	Odds Ratio
PCS	Physical Composite Score
PMTCT	Prevention of Mother-to-Child Transmission
RR	Risk Ratio
SD	Standard Deviation
SMS	Short Message Service
UNAIDS	Joint United Nations Programme on HIV/AIDS
WHO	World Health Organization

1. INTRODUCTION

1.1. HIV

Human immunodeficiency virus (HIV) is believed to have originated in Kinshasa, in the Democratic Republic of Congo around 1930, when HIV crossed species from chimpanzees to humans. The current epidemic did not start until the mid to late 1970s. In the 1980s in the United States, cases of Kaposi's sarcoma and pneumocystis carinii pneumonia were reported in young, previously healthy men, which ultimately led to the recognition of Acquired Immune Deficiency Syndrome (AIDS) as a disease. AIDS was found in every continent, and by the end of the decade, the World Health Organization (WHO) reported that there were 400,000 cases worldwide (1).

In 2017, there were 36.9 million (31.1 million - 43.9 million) people living with HIV (2). Groups at high risk of infection include men who have sex with men, people who inject drugs, female sex workers and transgender women. Almost 2 million people were infected with the virus in 2017 (1.8 million [1.4 – 2.4 million]); however, this is a 47% decrease since the peak of the epidemic in 1996 (2). Sub-Saharan Africa bears the brunt of the burden of the epidemic, with the largest number of people living with HIV. Both globally and in East and Southern Africa, there are increasing numbers of people on treatment. In 2017, 21.7 million (19.1 – 22.6 million) were accessing therapy (2). The scale-up of antiretroviral treatment (ART) programmes in South and East Africa over the last decade has led to 60% of those with HIV in the region being on treatment (3).

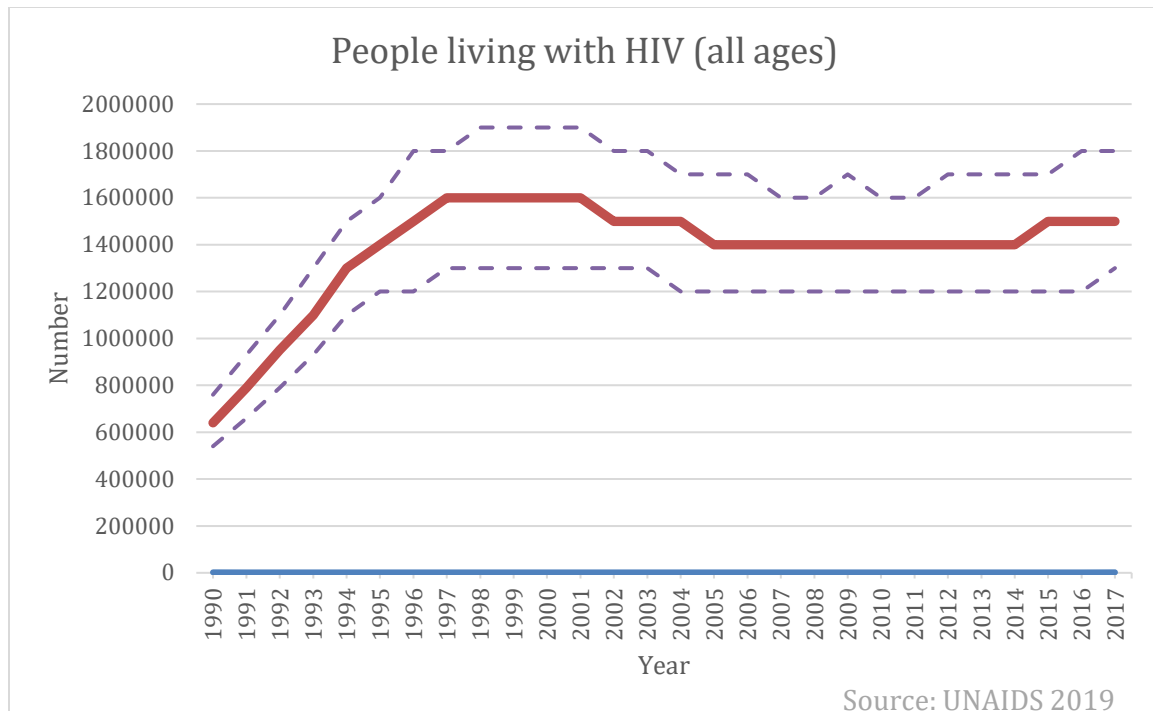
The Joint United Nations Programme on HIV/AIDS (UNAIDS) aims to end the AIDS epidemic by 2030. Concretely, by 2020, three targets have been set: to have 90% of people living with HIV know their status; 90% of those diagnosed with HIV on ART; and 90% of people receiving ART virally suppressed (4). To meet the first target, more frequent testing is required, as well as testing targeted to key populations and broader testing services, such as integrating testing with other care services and self-testing. Once people are aware of their status, it is critical to treat people with HIV. ART prevents illness and death, averts new infections, and has substantial economic benefits (through preventing new infections, increased labour productivity, and decreased need for orphan care and medical costs). To achieve the 3rd 90, long-term retention in care is essential, including re-engaging those who drop out of care.

1.2. HIV in Kenya

The first case of HIV in Kenya was detected in 1984. Towards the end of 1987, HIV began to spread rapidly, and by 1999, HIV was declared a national disaster. Currently, Kenya has the fourth largest HIV epidemic in the world. In 2017, there were 1.5 million (1.3– 1.8 million) people living with HIV in the country (Figure 1), with a prevalence of 4.8% (4.0 – 5.8%) among adults aged 15 to 49 years (5). HIV infection is more prevalent in women than men throughout Africa, and in Kenya 860,000 (730,000 - 1,000,000) women are living with HIV compared to 520,000 (430,000-630,000) men (5). More

women than men are also on treatment. In 2017, 65% (49 – 80%) women aged 15 years and older were receiving ART compared to 53% (38 – 66%) of men (UNAIDS 2019).

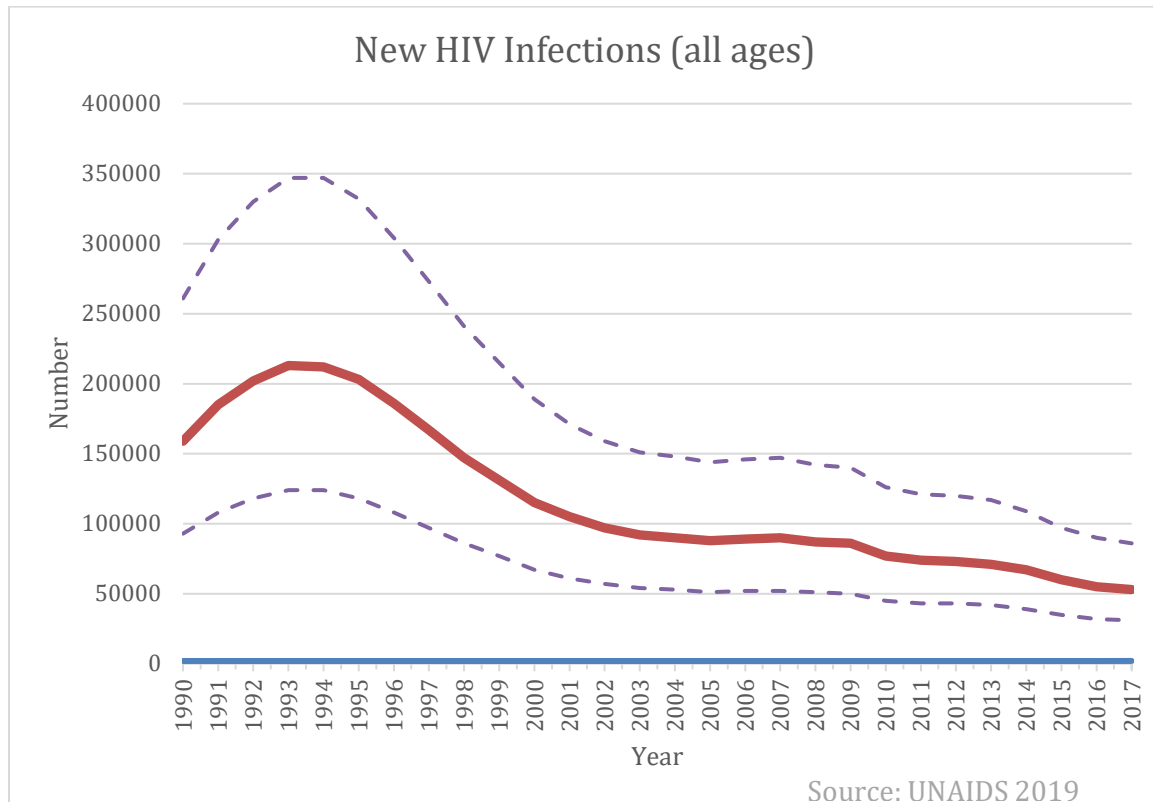
Figure 1. People living with HIV in Kenya



Kenya's epidemic, driven by heterosexual sexual transmission, is considered generalized as it is firmly established in the general population; however, there are groups who are especially vulnerable to infection. The groups most affected include female sex workers; men who have sex with men; people who inject drugs; and adolescents and young people (age 15 to 24 years), particularly women. Forced sex and sexual violence have made young women vulnerable to HIV infection (6). Compared to adults, the likelihood of adolescents and young people initiating and staying on treatment is low, and AIDS remains the leading cause of death in Kenya among young people (7). Female sex workers, men who have sex with men, and people who inject drugs face stigma, discrimination and violence in Kenya. Stigma and the criminalization of homosexuality are barriers to seeking treatment for people with HIV, and often for health care workers providing care to members of these groups.

HIV prevalence also varies geographically, from a high in Homa Bay County in the Nyanza region of 26% to a low in Wajir County in the North East region of 0.4% (8). Prevalence also varies between urban and rural areas, with a higher prevalence in urban areas. Within urban areas, differences are found between slum and non-slum populations. In Nairobi, 12% of slum residents are HIV positive compared to 5% of non-slum residents, and the gap in HIV prevalence between males and females narrows in slum areas (9).

Figure 2. New HIV infections in Kenya over time

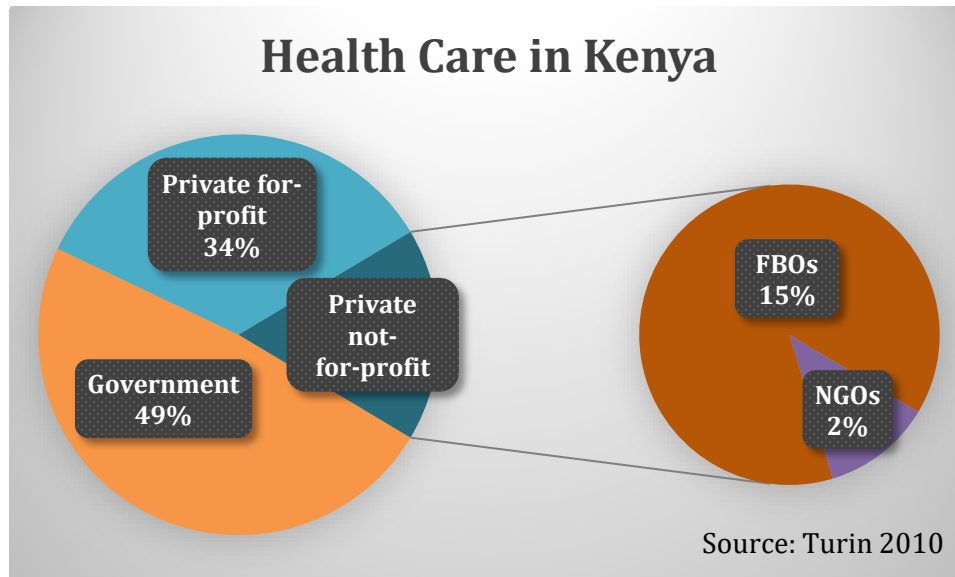


Between 2010 and 2017, there was a 32% reduction in new infections (Figure 2) and a 48% reduction in AIDS-related deaths (5). This is due to treatment and the success of several prevention programmes in Kenya, including condom availability and use, prevention of mother-to-child transmission programmes (PMTCT), HIV education and awareness, voluntary male circumcision and pre-exposure prophylaxis. For Kenya to continue to curb the HIV epidemic, stigma and discrimination need to be reduced, successful HIV prevention and treatment programmes require scaling, and sustainable funding must be ensured.

Health Care in Kenya

In Kenya, there is a mix of the private and public health care (Figure 3). The public sector is run by the Ministry of Public Health and other government institutions. The private sector is made up of for-profit and not-for-profit organizations, including local and international non-governmental organizations (NGOs), faith-based organizations (FBOs) and community-based organizations (CBOs). Private hospitals are found mainly in Nairobi and Mombasa, with private clinics found in most urban centres.

Figure 3. Health care in Kenya



Government-provided health care consists of hospitals, health centres, dispensaries and community health units (Figure 4). Hospitals offer curative services while at the sub-district level, health promotion and prevention services are offered. The district hospitals are the first referral centre. Health centres are typically staffed by midwives, nurses, clinical officers and occasionally physicians. These centres offer basic curative, preventative and reproductive health services. Dispensaries are run by registered nurses. There are also traditional medicine practitioners and individuals and communities who ensure care and support for their families and their broader community.

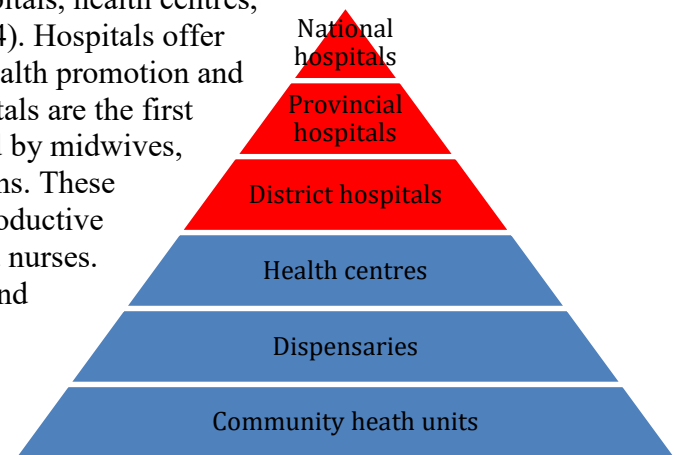


Figure 4. Hierarchical structure of healthcare in Kenya

HIV puts on enormous strain on Kenya's healthcare system and is the leading cause of death. HIV and AIDS are the reason for more than half of all hospital admissions (9).

Kenya's HIV response is still funded primarily by donors. There is a significant and growing funding gap to meet the UNAIDS 90-90-90 targets by 2020 as external funding is flat-lining or decreasing. This is despite the government of Kenya doubling its funding towards the HIV and AIDS response between 2007 and 2013 (10). In addition, Kenya is now classified as a middle-income country, which changes their eligibility for funding. To meet targets, the government of Kenya will need to substantially increase its allocation to the response (11), which may not be feasible. The government of Kenya needs to find options for sustainable funding and surmount inequities in healthcare provision in gender, between urban and rural populations, and between districts and provinces. At the same time, stigma and discrimination needs to be tackled and legal and structural barriers reduced.

1.3. Retention in HIV Care

Retaining individuals in care is fundamental to the long-term success of HIV programmes and to meet the UNAIDS 90-90-90 targets. Yet, over 20% of patients in ART programmes are lost to follow-up by six months in lower-income settings (12). In a systematic review of studies conducted in sub-Saharan African between 2007 and 2009, attrition at 12-months remained at 20% but by 36 months, increased to 35% (13). Among patients who have not yet initiated treatment, retention is even worse (14, 15). Retaining ART-ineligible patients is critical to reduce the high risk of morbidity and mortality in this population and to minimize the risk of late treatment initiation. Furthermore, patient retention is associated with decreased transmission risk behavior (16) and has the potential to contain health care costs (by capturing individuals before they are in need of hospital care).

At the time these studies were undertaken (under the umbrella of the WelTel Retain trial designed to investigate the effect of text-messaging on retention in early HIV care), WHO's guidelines were to initiate ART when an individual's CD4 count dropped below 350 cells/mm³. In 2013, during the trial, WHO changed the guidelines so that people with higher CD4 counts (500 cells/mm³) were eligible for treatment. In 2016, after the trial was complete, WHO revised guidelines to recommend that all individuals initiate ART, regardless of their CD4 count. Retention in care among individuals with HIV, irrespective of their position along a changing continuum of care, is imperative to prevent transmission of the virus, reduce morbidity and improve survival.

Barriers to retention in HIV Care

There are many social, structural and personal barriers to retention in HIV care. Transportation costs and geographical distance (17, 18) to clinic are factors, which are more prevalent in rural compared to urban areas and are compounded by poor terrain and a lack of transportation infrastructure (19). Social barriers include stigma, discrimination and a lack of social support (20). Many people do not want to be seen by people who they know when they are receiving care from a HIV clinic, so they often travel farther to receive care from clinics outside of their community. Barriers at the clinic include negative interactions with healthcare providers, who may be rude, unfriendly, disrespectful and patronizing. Other clinic-related barriers include long waiting times to see a clinician or to receive test results, concerns regarding healthcare providers maintaining confidentiality, and overcrowding (19).

People with HIV may also have competing priorities. Attending clinic appointments may mean missing time from work, caring for children and domestic responsibilities, which may be a larger barrier to retention in care among poor families. A lack of status disclosure to a partner and family is associated with poor retention (18). Many males are

migrant workers, and travel as truck drivers, fishermen or farm workers, making attending the clinic for regular appointments more difficult (18). Drug and alcohol use is a barrier to retention in HIV care, as are misconceptions about HIV care and treatment (20). Feeling healthy and well is another reason people do not return to clinic (21), and conversely, ART toxicity and poor health is also a factor (18).

Retention in clinic versus retention in care

There have been several studies and reviews estimating retention in ART care in sub-Saharan Africa (13,22,23), and to a lesser extent, retention in pre-ART care (14,23,24). Authors of these reviews have noted limitations of the included studies such as not counting patients who drop out of care and re-enter the health system, lack of reporting of transfers out of care (either formally or informally), and not tracing patients who are lost to follow-up to ascertain their status. These limitations may lead to an underestimate of retention in HIV care. More accurate estimates of retention in care require moving beyond quantifying whether individuals return to the clinic at which they originally enrolled (*retention in clinic*) to examining whether participants who did not return to the clinic are active in care at their original clinic or elsewhere (*retention in care*).

Around the time we designed our cohort study to estimate retention in care, a study in rural Uganda using a sampling-based approach to estimate retention in HIV care beyond those who simply returned to the clinic was published (25). In this study, around 15% of the 829 participants deemed lost to follow-up were traced to ascertain their vital status (25). Two scenarios, an “optimistic” scenario in which traced patients found alive, but not interviewed, were assumed to be active in care, and a “pessimistic” scenario in which traced patients found to be alive, but not interviewed, were assumed to be inactive in care, demonstrated increased estimates of patient retention in care at one, two and three years compared to estimates based on *retention in clinic* alone (25). Since then, additional studies have documented the importance of using *retention in care*, which accounts for informal and formal transfers, rather than *retention in clinic*, when quantifying retention in HIV care (21,26)

1.4. Mobile phones and retention in care

Most mobile health (mHealth) studies in HIV care have focussed on using text messages to promote medication adherence. Although findings have been mixed, findings from meta-analyses indicate that overall, weekly text-message interventions improve adherence (27). Results from meta-analyses also indicate that less frequent messaging and messaging that requires a response from participants is more likely to be effective than both more frequent messaging and messages that do not require a response (27–29).

There have been few studies of mHealth interventions to improve retention in HIV care. Most of the mHealth studies that have been done, both in and outside of Africa, have investigated text messages as appointment reminders rather than as a tool to improve retention in HIV care. Studies using one-way text message appointment reminders e.g. “Remember you have an appointment tomorrow.” failed to demonstrate an effect on

appointment attendance (30–33). Several of the studies suffered from methodological limitations, including small sample size (33), presenting data on individuals with HIV as a subgroup (32), a before-and-after study design (32), and selection bias (33). Conversely, two randomized controlled trials of women enrolled in PMTCT programmes in Kenya found that fortnightly mobile phone calls or supportive text messages (in which participants were given the opportunity to respond) improved retention in care (34,35). To my knowledge, the WelTel Retain trial was the first study in a resource-limited setting to test whether an interactive text-messaging service improved retention in care in a general population with HIV.

2. AIMS AND OBJECTIVES

2.1 Overall aim

Quantify retention in care considering informal and formal transfers of care and determine whether a text-messaging intervention promotes retention in care during the first year of HIV care in low-income settings in Kenya.

2.2 Specific objectives

1. To determine whether advanced HIV at presentation to care is due to late diagnosis or delays in accessing care and factors associated with it. (Study I)
2. To determine if there are gender differences in health-related quality of life (HRQoL) among adults at the time of a positive HIV test and to examine gender-specific factors associated with HRQoL. (Study II)
3. To quantify retention in clinic versus retention in care during the first year of HIV care and determine risk factors associated with attrition from care in low-income settings in Nairobi, Kenya. (Study III)
4. To determine whether a two-way text-messaging intervention improves retention during the first year of HIV care in Nairobi, Kenya. (Study IV)

3. METHODS

3.1 Study design

Studies I and II

Studies I and II are analytical cross-sectional studies. They both used questionnaire data collected through face-to-face interviews and laboratory data collected at the baseline visit. Study I compared those with advanced HIV to those with non-advanced HIV at presentation to care. Study II compared self-perceived health-related quality-of-life data collected at the time of presentation to HIV care between men and women.

Study III

Study III is a cohort study that followed adults who tested positive for HIV from their baseline visit for up to 14 months. After examining study records, those who did not return to care were contacted by telephone or traced in the community. Those who were retained in care at one year versus those who were not were quantified and compared.

Study IV

Study IV is an unmasked, randomised, parallel-group study conducted at two clinics in informal settlements in Nairobi, Kenya. The trial examined whether a text-messaging intervention improved retention in HIV care at 12 months.

3.2 Setting

The study was initially designed as a single-site study in Kibera, an informal settlement in Nairobi, Kenya. Entry to the study required a positive HIV test. A series of nationwide shortages of HIV test kits led to slower-than-expected recruitment. To complete the study on time and within budget, we added a second site in Baba Dogo, which is another informal settlement in Nairobi.

Kibera is the largest slum in Nairobi, covering 2.38 km². The population of Kibera is 170,070 according to the 2009 Kenyan census (36), although estimates vary widely. Baba Dogo is in Nairobi's Eastlands area. It is smaller than Kibera with a population of approximately 30,000 (37).

Both informal settlements lack government health care and their populations have minimal access to basic services such as education, water, sanitation, transportation infrastructure and other public services. Unemployment in both Kibera and Baba Dogo is high, and there is overcrowding and insecurity. HIV prevalence among adults in Kibera is 12% (38) compared to 5% among Nairobi's non-slum residents (39).



Figure 5. Outside the Kibera Community Health Centre

Between April 4th, 2013 and June 4th, 2015, we recruited participants from the Kibera Community Health Centre, operated by Amref Health Africa, the largest non-governmental health organisation based in Africa (<https://amref.org/home/>). On Feb 26th, 2014, recruitment began at the Baba Dogo Health Centre, operated by Partners for Health and Development in Africa, a non-profit organisation registered in Kenya and affiliated with the University of Manitoba. Recruitment at this site ended on May 27th, 2015. Both clinics are primary comprehensive care clinics, with no direct patient costs for HIV or AIDS care and treatment.

Participants were followed up for up to 14 months. Follow-up concluded on September 22nd, 2016. Data were collected throughout the follow-up period.

3.3 Participants

Individuals who tested HIV-positive at the Kibera and Baba Dogo Health Centres were referred to a research nurse, who assessed study eligibility using a checklist.

Eligibility criteria for the trial (Study IV) are listed below.

Inclusion criteria:

- HIV positive;
- at least 18 years of age;
- own or have access to a mobile phone and be able to use simple text messaging (or have somebody who could text message on their behalf).

Exclusion criteria:

- previous assessment for ART eligibility;
- previous or current exposure to ART;
- pregnancy.

If a person met all the criteria except for the phone-related criteria, they were invited to participate in a supplementary cohort study (described below). Studies I, II, and III included all the participants enrolled in the randomised controlled trial as well as participants enrolled in the supplementary cohort study.

3.4 Supplementary cohort study

At the time of recruitment, if potential participants did not meet the trial's phone-related criteria (i.e. own or have access to a mobile phone and be able to use simple text messaging [or have somebody who could text message on their behalf]), they were invited to enrol in a supplementary cohort study. The rationale for establishing a larger cohort involving participants who were not eligible for the trial was to establish a more generalizable cohort for ancillary studies than that which would have been established if we had used the trial population alone. Participants in the cohort study were not randomized to the intervention or control arm but underwent the same procedures as trial participants e.g. consent procedures, questionnaires, and tracing if they did not return to the clinic at 12 months.

3.5 Intervention and randomization

Participants were randomly assigned to receive the intervention in addition to usual care or to usual care only. Individuals participating in the cohort study only were not randomised and did not receive the intervention.

The WelTel service consisted of weekly text-messages to check-in on how patients were doing and provide them the opportunity to identify whether assistance was required (Figure 6). Every Monday morning, a short message service (SMS) gateway sent text messages to intervention arm participants asking “Mambo?” (Swahili for “How are you?”). Participants were instructed to respond within 48 hours of receiving the message either that they were well (e.g. “Sawa”—Swahili for okay) or that they were having difficulties (e.g. “Shida”—Swahili for difficulty). The research nurses telephoned all participants who reported a problem or did not respond and recorded participants' issues and reasons for non-response. Intervention arm participants received the intervention until

the earliest of the following: death; study withdrawal; or study exit.

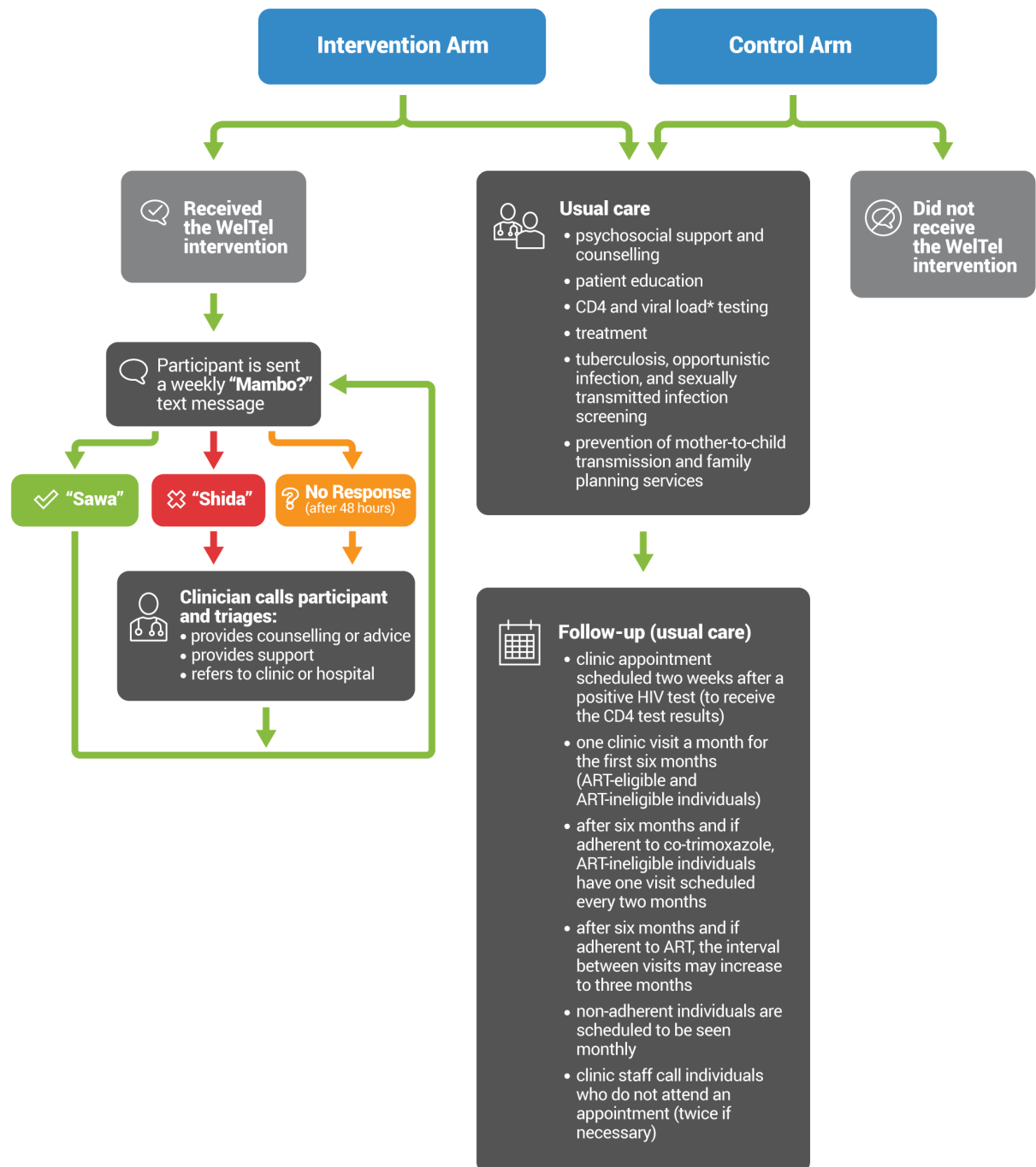
Randomization and allocation

Randomization of participants to the intervention or control arm was at a 1:1 ratio, using random block sizes of 2, 4 and 6. Block sizes were not disclosed until publication of the trial. We generated the randomisation sequence using the “ralloc” command in Stata. A research assistant put the allocations in individual, sequentially numbered, opaque envelopes and sealed them. After meeting inclusion criteria, consenting to participate, and completing baseline assessments, participants were assigned to a study arm by a research nurse who opened one of the numbered envelopes to determine allocation.

Usual care

Control arm and cohort-study-only participants did not receive text messages from the automated WelTel service. Participants in the control and intervention groups, as well as the cohort-study-only participants, received usual care and were followed-up according to clinic protocol (Figure 6). Baseline laboratory testing include two rapid HIV tests. The first was Alere Determine HIV-1/2 (<https://www.alere.com/en/home/product-details/determine-hiv-1-2.html>). Uni-Gold (<http://www.trinitybiotech.com/area/uni-gold/>) was used as a confirmatory test. CD4 counts were measured at the baseline visit and throughout the study. Among other services, usual care included psychosocial support and counselling, patient education, and treatment (Figure 6). Patients who did not attend a clinic appointment were called one day after a missed appointment, and if necessary, they were called a second time three days later.

Figure 6. Intervention and Usual Care



3.6 Data collection

Experienced HIV research nurses were hired specifically for the project. Data were collected using study-specific instruments as well as part of routine care. After a confirmatory HIV test, the research nurses used an eligibility checklist to determine if a potential participant was eligible for the trial or supplementary cohort study. If an individual was eligible and willing to participate, the research nurse went through the consent forms with the participant and collected either written consent (if literate), or a thumbprint with a witness's signature if illiterate. A piloted, validated questionnaire was then administered by the research nurse. The research nurses also completed a detailed participant locator form. The participants had the choice of conversing in English or Kiswahili.

Baseline CD4 data reflecting the immune status of the participants were taken from routine data in clinical records. Throughout the study, CD4 count for each test and visit date data were also collected. Partway through the study, the clinics began viral load testing (October 2014 in Kibera and February 2015 in Baba Dogo). Viral load data were collected but not used in any of the studies.

At six and 12 months, study-specific follow-up questionnaires were administered for all participants who returned to the clinic at these time points. At the end of the study, a tracing report form was filled out for all participants, indicating whether they returned to the clinic or if they did not, what type of tracing was undertaken to ascertain their status (telephone or community tracing). This form reported the participants' final outcome i.e. retained in clinic, informally or formally transferred care, lost to follow-up, or death.

Before the study began, the questionnaire was translated from English to Kiswahili, back-translated, and pre-tested with clinic patients ($n = 10$). Previously validated instruments were used when possible, e.g. the SF-12 health-related quality of life questionnaire previously validated in a similar setting. Throughout the study, data were entered in Microsoft Access on a weekly basis. Verification procedures included cross-checking data files with original forms and clinical records, as well as range and consistency checks.

For participants receiving the WelTel intervention, WelTel's technological platform captured outgoing weekly SMS messages and incoming participant responses and instances of non-response. The research nurses used the platform to record reasons why a participant responded with a problem or did not respond, and the actions that were taken.

3.7 Ethical considerations

Consent was sought from all participants in the trial and supplementary cohort study. After a clinic staff member introduced the study to the potential participant, a trained research nurse provided the potential participant with further details. If the participant wanted to enrol, the research nurse discussed the information in the consent form with them in the language in which the individual was most comfortable, English or Kiswahili.

Participants were given the opportunity to ask questions before providing written consent. Once signed, each participant was provided with a copy of the information and consent form. Illiterate patients who wished to participate provided consent in the presence of a literate witness; the participant's thumb print was used in lieu of their signature.

As the study involved tracing participants by telephone or in their communities to determine their status at the end of the study, special ethical consideration was required. Aspects of the study that were unusual for research studies, i.e. including identifying information on study records, such as locator forms that were disseminated to outreach healthcare workers, needed to be explicitly stated on consent forms.

The original study protocol, information and consent form, and baseline questionnaire were approved by the University of British Columbia Clinical Research Ethics Board (H12-00563) and the AMREF Ethics and Scientific Review Committee (P40/12). Ethical approval was renewed on an annual basis.

3.8 Outcomes

Table 1. Outcomes, outcome measures and methods of analysis for all four studies

Outcome	Outcome measure	Method of analysis
Study I		
Advanced HIV	Presenting with a CD4 count <200 cells/mm ³ or at WHO stage 4	i. Descriptive statistics ii. Logistic regression to examine factors associated with advanced HIV
Study II		
Health-related quality of life	SF-12 PCS and MCS scores	Multiple linear regression
Study III		
a) 12-month retention in clinic	Attends 12-month clinic appointment at the clinic at which participant originally enrolled (10-14 month timeframe)	Descriptive statistics
b) 12-month retention in care	Attends 12-month clinic appointment at the clinic at which participant originally enrolled or active in care elsewhere (10-14 month timeframe)	i. Descriptive statistics ii. Generalized linear regression to examine factors associated with attrition (those not retained in care were considered lost to attrition)
Study IV		
1.Primary outcome:		
a) 12-month retention in care	Attends 12-month clinic appointment (10-14 month timeframe) or active in care elsewhere	Chi-squared test

2. Key secondary outcomes:		
a) Retention in Stage 1 HIV care	Attends clinic to receive CD4 results (within 3 weeks of positive HIV test)	Chi-squared test
3. Additional secondary outcomes:		
a) Timely initiation of ART	Starts ART within 3 months of eligibility (for those eligible at baseline)	Chi-squared test
b) Time to ART initiation	ART initiation after eligible (at baseline)	Kaplan-Meier survival analysis
c) 6-month retention in clinic	Attends 6-month clinic appointment (5-7 month timeframe)	Chi-squared test
d) 12-month retention in clinic	Attends 12-month clinic appointment (10-14 month timeframe)	Chi-squared test
e) Proportion of scheduled appointments kept	Mean proportion of scheduled appointments attended	T-test
f) Satisfaction with care	5-point Likert scale item	Kruskal-Wallis test
g) Level of social support	5-point Likert scale item	Kruskal-Wallis test
h) Health-related quality of life	SF-12 PCS and MCS scores	T-test
i) Death (all-cause)	All-cause mortality (binary)	Chi-squared test

3.9 Statistical Methods

Each study included descriptive statistics of participants' baseline characteristics to enable comparison of groups. These statistics were reported as a mean (SD) or median (first quartile, third quartile) for continuous variables, and count (percent) for categorical variables. Baseline characteristics included: gender, age, education, CD4 count, ART eligibility, mobile phone access, and other variables relevant to the study. In all studies, descriptive analyses were conducted in SPSS versions 14 or 21, and additional analyses were completed using Stata version 12. Analyses were restricted to individuals with complete data and all *p*-values are two-sided.

Study I

Logistic regression was used to determine factors associated with advanced HIV at presentation to care. First, univariable analyses were performed to assess the strength of the association between each factor and the outcome. Variables were then included in an initial multivariable model if they had a univariable *p*-value of ≤ 0.25 or were considered important based on prior evidence (i.e. sex). In the final adjusted models, variables were selected based on a significance threshold of $p < 0.05$. Nested models were compared using likelihood ratio tests to examine interaction between sex and travel time, and to determine whether to include a linear effect or indicator variables for ordered categorical variables. The fit of the final model was tested with the Hosmer-Lemeshow goodness-of-

fit test. Results are presented as estimated odds ratios (OR) and adjusted ORs (AOR) with corresponding 95 % confidence intervals (CI) and *p*-values. All *p*-values are two-sided and reported to three decimal places with those less than 0.001 reported as $p < 0.001$.

Study II

Multiple linear regression was used to determine whether gender was associated with HRQoL. Univariable analyses were performed to assess the strength of the association between each factor and the outcome. Variables were included in an initial multivariable model if they had a univariable *p*-value of ≤ 0.25 or were considered important based on prior evidence. Variables included in final adjusted models were selected based on a significance threshold of $p < 0.05$; however, all variables strongly associated with the outcome in univariate analyses were also included.

Since gender-specific models were exploratory, all variables were included in the models. The adequacy of the models was evaluated by examining plots of the residuals. Heteroscedasticity was tested using Breusch–Pagan and White tests. Robust standard errors were used if heteroscedasticity was detected. Results are presented as the mean difference with corresponding 95% CI and *p*-values.

Study III

Generalized linear regression with a log link and binomial distribution was used to test whether selected factors were associated with attrition from care (rather than attrition from clinic). First, bivariate analyses were performed to assess the crude association between each factor and the outcome. Then, all variables were included in a multivariable model. Interaction between variables and tests of linear assumption (for variables with multiple categories) were examined using nested models and the likelihood ratio test. Results are presented as risk ratios (RR) and adjusted RRs (ARR) with corresponding 95% CI.

Study IV

Analyses were by intention to treat; therefore, we included all participants according to the study group to which they were originally allocated, regardless of the intervention received, or if they were subsequently deemed ineligible. For the primary and key secondary endpoints, we used a χ^2 test to determine if the proportions of participants retained in care differed between the study groups. Secondary binary outcomes were similarly analysed. For other secondary outcomes, we used *t*-tests for continuous variables and Kruskal–Wallis or Mann–Whitney *U* tests for non-normally distributed variables. For time-to-event outcomes, we used a Kaplan–Meier analysis and estimated the hazard ratio. We also assessed the proportional hazards assumption. In subgroup analyses, we assessed whether the intervention effect was homogeneous by including an interaction term between the intervention allocation and subgroup-defining variable. We reported *p* values for the interaction tests, rather than the treatment effect within groups.

3.10 My role in these studies

While working for Dr. Richard Lester in 2011, the National Institutes of Health issued an AIDS-related funding opportunity announcement for innovations to optimize HIV retention in care. On the heels of the successful WelTel Kenya1 trial, he decided to apply for funding to investigate whether WelTel may be an effective retention strategy earlier in the continuum of HIV care. I was responsible for writing the NIH grant, including designing the trial (in consultation with other investigators), calculating sample size, proposing statistical analyses (approved by the trial statistician), and writing exhaustive documents on ethical considerations and other NIH requirements.

When the scientists at NIH had reviewed our application, I was responsible for answering their queries. I consulted with other investigators when the questions lay beyond my realm of knowledge.

In conjunction with the WelTel Retain trial, I designed a supplementary cohort study to investigate retention in care without the limitations associated with using a trial population only. The baseline data from this larger cohort study was used to examine advanced HIV at presentation to care and health-related quality of life, the latter being Professor Ekström's idea.

I was responsible for the overall management of the trial, including liaising with the Data Safety and Monitoring Board and the multiple institutions involved. During the trial, I wrote an application for additional funding and managed the interim analysis. I visited Nairobi numerous times to have face-to-face contact with research staff and to better understand the context of the study. During the study, I was responsible for data oversight, including data cleaning.

For each study, I was principally responsible for design, statistical analysis, and writing the manuscript. In all instances, I submitted the manuscripts for publication and was responsible for making the required revisions in consultation with my co-authors and for the responding to the reviewers, which were quite the undertakings in the cases of the articles published in *Lancet Public Health* and the *Journal of the International AIDS Society*.

4. RESULTS

4.1 Advanced HIV disease at presentation to care: late diagnosis or delayed linkage to care? (Study I)

Of the 1068 HIV individuals living with HIV who were screened to participate in the study, 775 were recruited (700 for the trial and 75 for the cohort study only). Selected baseline characteristics are shown in Table 2. Approximately 1/3 (n=248/753; 32.9%) of the cohort presented to care with advanced HIV (CD4 count <200 cells/mm³ or WHO stage 4) (see appendix).

Table 2. Demographic and clinical characteristics of participants in the Advanced HIV study, n=753, Nairobi, Kenya.

Variable	Non-advanced HIV at presentation to care (n=505) n (%)	Advanced HIV at presentation to care (n=248) n (%)
Sex		
Male	183 (61.4)	115 (38.6)
Female	322 (70.8)	133 (29.2)
Age (years)		
Mean (SD)	32 (9.22)	37 (10.26)
<30	227 (79.9)	57 (20.1)
30-39	178 (62.9)	105 (37.1)
40-49	71 (57.7)	52 (42.3)
≥50	29 (46.0)	34 (54.0)
CD4		
Median (IQR) (cells/ mm ³)	389 (298-545)	90 (42-147)
≤350	210 (46.0)	247 (54.0)
>350	295 (99.7)	1 (0.3)
WHO Stage		
1	356 (78.1)	100 (21.9)
2	72 (63.7)	41 (36.3)
3	57 (39.9)	86 (60.1)
4	0 (0.0)	8 (3.2)
Missing	20 (60.6)	13 (39.4)
Previous HIV diagnosis		
No	199 (66.1)	102 (33.9)
Yes	306 (67.7)	146 (32.3)

Abbreviations: SD=standard deviation, IQR=interquartile range.

Late diagnosis versus delayed presentation to care

Of those who presented to care with advanced HIV, 146 (n=59%) had been previously diagnosed with HIV elsewhere. This was similar to the proportion of those with a

previous diagnosis in the non-advanced HIV group (n=306/505; 61%; chi-square *p*-value 0.650). Most participants with advanced HIV presented to care within three months of their initial diagnosis (102/145; 70%), including 44 individuals who presented within one week. The median time to presentation to HIV care after an initial diagnosis was 22 days (IQR 6-147) for those with advanced HIV, compared to 19 days (IQR 4-119) for those with non-advanced HIV (*p*=0.716).

Factors associated with presentation to care with advanced HIV

Table 3 shows the association between clinical and sociodemographic characteristics and presenting to care with advanced HIV. In both univariable and multivariable analyses, age was linearly associated with presenting to care with advanced HIV, with a final AOR of 1.72 (95% CI 1.42 to 2.03) per unit increase in age category, compared to the reference category of <30 years. Individuals presenting to the Baba Dogo clinic were more likely to present with advanced HIV (AOR 1.55; 95% CI 1.09-2.20) than those presenting to the Kibera clinic. Participants with some secondary education were less likely to present with advanced HIV; however, this association was of borderline significance in the final model (AOR 0.73; 95% CI 0.53-1.03). In the univariable analysis, male sex appeared to be associated with presenting with advanced HIV; however, this effect diminished in the multivariable analysis and did not remain in the final model.

Table 3. Univariable and multivariable analysis of variables associated with presentation to care with advanced HIV disease, Nairobi, Kenya.

Variable	Crude ORs				Adjusted ORs				Final adjusted ORs		
	OR	95% CI	p-value		OR	95% CI	p-value		OR	95% CI	p-value
Age*	1.66	1.41-1.96	<0.001		1.65	1.39-1.97	<0.001		1.72	1.45-2.03	<0.001
Presenting at the Baba Dogo clinic	1.23	0.88-1.71	0.220		1.53	1.08-2.17	0.018		1.55	1.09-2.20	0.014
Secondary education	0.74	0.53-1.03	0.070		0.69	0.49-0.98	0.040		0.73	0.52-1.03	0.073
Male gender	1.52	1.12-2.07	0.008		1.30	0.93-1.82	0.128				
Illicit drug use	0.60	0.30-1.20	0.155		0.53	0.26-1.09	0.084				
Hazardous drinking	1.04	0.74-1.44	0.835								
Travel time†	0.98	0.84-1.34	0.782								
Previous HIV diagnosis	0.93	0.68-1.27	0.650								

Abbreviations: OR, odds ratio, CI, confidence interval.

* OR corresponds to an increase in the odds ratio per unit increase in category

4.2 Gender differences in health-related quality of life at the time of a positive HIV test (Study II)

Of 1068 HIV-positive individuals screened to participate in the study, 775 were recruited (700 for the trial and 75 for the cohort study only). Selected baseline characteristics are shown in Table 4. Women comprised 61% of the cohort (n=470/775). Of the recruited participants, 752 (97%) had complete baseline questionnaire, CD4, and SF-12 data.

Table 4. Demographic and clinical characteristics of participants in the Health-Related Quality of Life study, n=775, Nairobi, Kenya.

Variable	Women (n=470) n (%)	Men (n=305) n (%)
Age (years)		
Mean (SD)	32 (9.21)	37 (9.77)
Education		
No secondary level	338 (71.9)	183 (60.0)
At least some secondary	132 (28.1)	122 (40.0)
Employment status*		
Employed	295 (71.1)	283 (93.1)
Unemployed	120 (28.9)	21 (6.1)
CD4 (cells/mm ³)		
Median (IQR)	328 (168-493)	266 (135-434)
Missing	15 (3.2)	7 (2.3)
Psycho-social support		
None/little/some of the time	98 (20.9)	57 (18.7)
Most or all of the time	372 (79.1)	248 (81.3)
Alcohol use		
Non-heavy/hazardous drinking	409 (87.0)	222 (72.8)
Heavy/hazardous drinking	61 (13.0)	83 (27.2)
Illicit drug use		
Not a current drug user	455 (96.8)	272 (89.2)
Current drug user	15 (3.2)	33 (10.8)

Abbreviations: SD=standard deviation, IQR=interquartile range.

*Does not include participants who are students (n=9) or homemakers (n=47).

Gender differences in mental and physical composite scores

The mean physical composite score (PCS) was higher in women than men (43.80 v 41.44, mean difference 2.36, 95% CI 0.61 to 4.11). After adjustment for confounding, the mean difference in PCS score increased marginally (mean difference 2.49, 95% CI 0.54 to 4.44) (Table 5). While statistically significant, this difference is not considered clinically important.

Women had a lower crude mean mental composite score (MCS) score than men, but this difference was neither statistically nor clinically significant (51.98 v 53.25, mean difference -1.27, 95% CI -2.88 to 0.33). After adjusting for confounding, the mean difference was reduced (mean difference -0.99, 95% CI -2.71 to 0.73).

Table 5. Unadjusted and adjusted differences in mean mental (MCS) and physical composite scores (PCS) (95% confidence interval) between men and women at the time of a positive HIV test, Nairobi, Kenya.

Outcome	No.	Mean score	Crude analysis	p-value	Adjusted for confounding	p-value
MCS						
Women	470	51.98	-1.27 (-2.88 to 0.33)	0.119	-0.99 (-2.71 to 0.73)	0.259
Men	304	53.25				
PCS						
Women	470	43.80	2.36 (0.61 to 4.11)	0.008	2.49 (0.54 to 4.44)	0.012
Men	304	41.44				

Abbreviations: MCS=mental composite score CI=confidence interval.

PCS score adjusted for age, baseline CD4, study site, education, employment, marital status (adjusted model n=698). MCS score adjusted for employment, site, baseline CD4, social support, and current drug use (adjusted model n=698)

Gender-specific factors associated with Health-Related Quality of Life

Few of the factors investigated were associated with MCS in the sex-specific HRQoL analysis. For both men and women, being unemployed was associated with a clinically important decrease in MCS (men: -5.13, 95% CI -10.02 to -0.23; women -3.98, 95% CI -6.43 to -1.54). There were no other factors significantly associated with men's MCS. For women, there was a 1.42 linear increase in score per increase in CD4 category. Social support was also a factor in women's MCS score, with those who felt that they had no to little social support having a lower score than those with greater social support (coefficient -2.77; 95% CI -5.46 to -0.08).

Several factors were associated with physical HRQoL, and the same factors were associated with PCS in both men and women. Older age and unemployment were associated with a decrease in PCS; while having attended at least some secondary school and having a higher CD4 was associated with an increase in PCS. The effect of these factors were in the same direction and of similar magnitude for both men and women, apart from employment status, where being unemployed was associated with a larger

decrease in PCS for males than for females (males -6.90, 95% CI -11.60 to -2.20 v. females -3.05, 95%CI -5.56 to -0.54).

4.3 Retention in clinic versus retention in care during the first year of HIV care (Study III)

This study also involved the 700 participants recruited for the trial as well as 75 participants ineligible for the trial, but eligible for the cohort study. Retention in clinic was defined as returning to the same clinic at which participants enrolled between 10 and 14 months. Retention in care was defined as being active in HIV care at any clinic 10 to 14 months after enrolling in HIV care.

$$\text{retention in care at 12 months} = \frac{\text{participants retained in clinic} + \text{participants confirmed active in care elsewhere}}{\text{all enrolled study participants}}$$

Selected baseline characteristics categorized by those who were lost to care and those who were retained in care are found in Table 6.

Table 6. Demographic and clinical characteristics of participants in the Retention in Care study, n=775, Nairobi, Kenya.

Variable	Attrition from care at 12-months (n=166) n (%)	Retained in care at 12-months (n=609) n (%)
Sex		
Male	74 (24.3)	231 (75.7)
Female	92 (19.6)	378 (80.4)
Age (years)		
Mean (SD)	34.7 (10.8)	33.7 (9.5)
Education		
No secondary school	120 (23.0)	401 (77.0)
Some secondary school	46 (18.1)	208 (81.9)
Previous HIV diagnosis		
No	72 (22.4)	249 (77.6)
Yes	94 (20.7)	360 (79.3)
CD4 (cells/mm ³)		
Median (IQR)	252 (84-450)	314 (168-464)
Missing	12 (54.54)	10 (45.45)
ART eligibility at baseline		
Ineligible	43 (19.6)	176 (80.4)
Eligible	111 (20.8)	423 (78.2)
Missing	12 (54.54)	10 (45.45)
Trial participant		

No	28 (37.3)	47 (62.7)
Yes	138 (19.7)	562 (80.3)
Travel time to clinic		
<60 minutes	97 (16.1)	507 (83.9)
≥60 minutes	23 (19.2)	97 (80.8)
Missing	1	5

Abbreviations: SD=standard deviation, IQR=interquartile range

Retention in clinic versus retention in care

Overall, 486/775 participants (62.7%, 95% CI 59.2% to 66.1%) were retained in clinic at 12 months (returned to the clinic for their 12-month visit between 10 and 14 months), whereas 609/775 (78.6%, 95% CI 75.7% to 81.5%) were retained in care at 12 months (returned to the clinic for their 12-month visit or were confirmed active in care elsewhere).

Factors associated with attrition from care

In the crude analysis, presenting at the Baba Dogo clinic and being a trial versus a cohort study participant were associated with a reduced risk of attrition. In the multivariable model, being a trial participant remained strongly associated with a reduced risk of attrition (ARR 0.52, 95% CI 0.37 – 0.73). Compared to the baseline CD4 count category of 200 cells/mm³, participants in higher CD4 count categories had a reduced risk of attrition (ARR 0.59, 95% CI 0.40 – 0.85) for those in the 200-349 cells/mm³ CD4 count category, and ARR 0.61 (95% CI 0.35 – 1.08) for those in the 350-499 cells/mm³ CD4 count category. An interactive effect between sex and travel time to clinic was not found.

4.4 Effect of an interactive text-messaging service on patient retention during the first year of HIV care (Study IV)

Of the 1068 participants screened for study participation, 700 participants were recruited for the trial (Figure 7). All 349 participants allocated to the intervention arm received the intervention, as well as one control arm participant. The analysis was intention to treat.

Figure 7. WelTel Retain trial: participant flow diagram

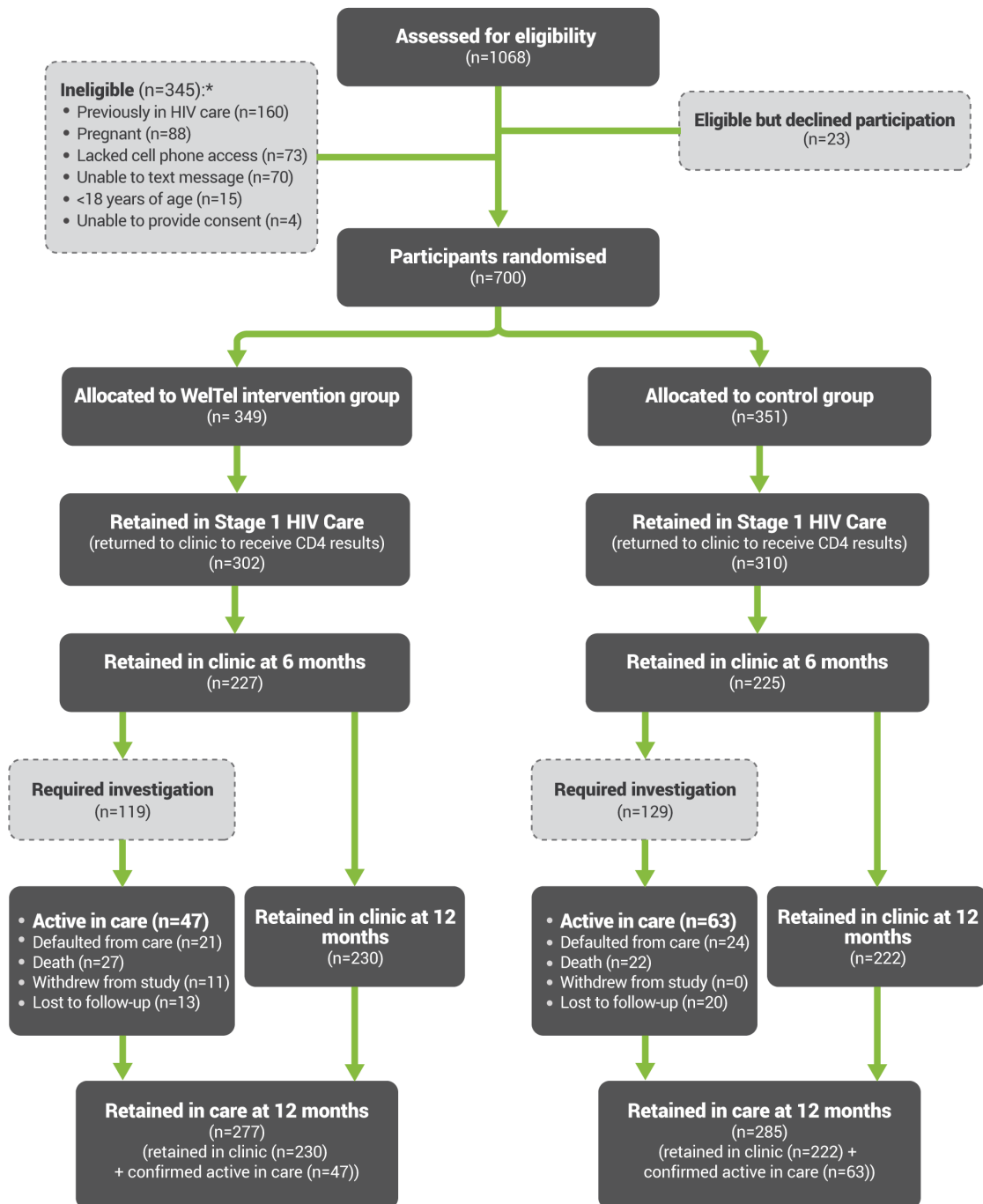


Table 7. Demographic and clinical characteristics of participants in the WelTel Retain trial, n=700, Nairobi, Kenya.

Variable	Control (n=351) n (%)	SMS intervention (n=349) n (%)
Sex (female)	213 (60.7)	206 (59.0)
Age (years) mean (SD)	33.46 (9.44)	33.99 (10.07)
Education		
No formal education	9 (2.6)	12 (3.4)
Primary	223 (63.5)	210 (60.2)
Secondary	119 (33.9)	127 (36.4)
Marital status		
Single	54 (15.4)	56 (16.0)
Married	206 (58.7)	193 (55.3)
Widowed or divorced	91 (25.9)	100 (28.7)
Clinic		
Kibera	250 (71.2)	251 (71.9)
Baba Dogo	101 (28.8)	98 (28.1)
Previously diagnosed with HIV	199 (56.7)	212 (60.7)
WHO Stage		
1	226 (64.4)	206 (59.0)
2	47 (13.4)	54 (15.5)
3	61 (17.4)	62 (17.8)
4	1 (0.3)	7 (2.0)
Missing	16 (4.6)	20 (5.7)
CD4 (cells/mm ³) median (IQR)	307 (148-468)	289 (143-449)
Missing	8 (2.3)	10 (2.9)
ART eligible	237 (69.1)	251 (74.0)
HRQoL PCS, mean (SD)	42.59 (12.10)	43.12 (11.52)
HRQoL MCS, mean (SD)	52.13 (10.88)	53.23 (11.04)
Travel time to clinic		
<30 minutes	172 (49.0)	175 (50.1)
30-59 minutes	127 (36.2)	112 (32.1)
≥60 minutes	49 (14.0)	59 (16.9)
Missing	3 (0.9)	3 (0.9)
Own v. shared mobile phone	326 (92.9)	337 (96.6)

Abbreviations: SD=standard deviation, IQR=interquartile range, HRQoL=health-related quality of life

Primary and secondary outcomes

In the final analysis (n=700), the intervention had no effect on the primary outcome, retention in care at 12-months (risk ratio [RR] 0.98, 95% CI 0.91-1.05), nor did it have an effect on the key secondary outcome, retention in Stage 1 HIV care (RR 0.98, 95% CI 0.93-1.04) (Table 8). Similarly, the intervention had no effect on other retention or treatment outcomes such as the proportion of those who initiated treatment within three months, time to treatment initiation, or retention in clinic at six months (Table 8).

Table 8: Clinical outcomes of the WelTel Retain trial, Nairobi, Kenya.

	Intervention (n=349) n (%)	Control (n=351) n (%)	Risk ratio (95% CI)	Risk difference (95% CI)
Outcome				
Primary outcome				
Retained in care at 12-months	277 (79.4)	285 (81.2)	0.98 (0.91 - 1.05)	-0.02 (-0.08 – 0.04)
Key secondary outcome				
Retained in Stage 1* care	302 (86.5)	310 (88.3)	0.98 (0.93-1.04)	-0.02 (-0.07 - 0.03)
Secondary outcomes				
Initiated ART in a timely manner	207/251 (82.5)	186/237 (78.5)	1.05 (0.96 – 1.15)	0.04 (-0.03 - 0.11)
Retained in clinic at 6 months	227 (65.0)	225 (64.1)	1.02 (0.91 – 1.13)	0.01 (-0.06 – 0.08)
Retained in clinic at 12 months	230 (65.9)	222 (63.2)	1.04 (0.93 – 1.16)	0.03 (-0.04 – 0.10)
Death (all-cause)	27 (7.7)	22 (6.3)	1.23 (0.72 - 2.12)	0.02 (-0.02 – 0.05)

Abbreviations: CI=confidence interval

*participant returns to the clinic to receive the first CD4 count results

Satisfaction with care was similar between the two groups (Table 9). Although the median and interquartile range was the same in both groups for social support, intervention arm participants had a higher mean rank social support score than the control group (228.78 v. 206.97), indicating greater perceived social support in the intervention group (Table 9). PCS and MSC HRQoL scores were also greater in the intervention group than the control group, with a mean difference of 2.27 in PCS (95% CI 1.00 to 3.53) and 1.86 (95% CI 0.56 to 3.15) in MCS.

Table 9: Outcomes based on 12-month follow-up questionnaire data in the WelTel Retain trial, Nairobi, Kenya.

	Intervention (n=220)	Control (n=215)	Effect estimate (95% CI) or test statistic	p-value
Outcome				
Satisfaction with care* (median, Q1-Q3)	7 (7-7)	7 (7-7)	0.91 (Chi square)	0.34
Level of social support† (median, Q1-Q3)	5 (4-5)	5 (4-5)	4.91 (Chi square)	0.027
Health-related quality of life				
Physical composite score (mean, SD)	53.28 (4.68)	51.01 (8.32)‡	2.27 (0.10 to 3.53)	0.001
Mental composite score (mean, SD)	57.17 (5.53)	55.32 (7.97)‡	1.86 (0.56 to 3.15)	0.005

Abbreviations: CI=confidence interval, Q1-Q3=quartile 1-quartile 3, SD=standard deviation

*Kruskal-Wallis χ^2 (1 df) 0.912; control n=215 intervention n=220, mean rank control=213.80; intervention=222.11

†Kruskal-Wallis χ^2 (1 df) 4.910; control n=215 intervention n=220, mean rank control=206.97; intervention=228.78

‡n=214

Subgroup effects

There were no significant sub-group effects.

Adverse Events

An intervention arm participant had a mild adverse event related to the intervention, in a which their partner became suspicious of the weekly text messages and follow-up calls. They withdrew from the study.

Patient-perceived benefits and barriers to the intervention

Overall, most intervention arm participants who completed the follow-up questionnaire were pleased with the service and its frequency of delivery. Most (75% [n=165/220]) reported no barriers to the intervention. Barriers noted included lack of network credit (n=22/220, 10%) and phone access (n=12/220, 5.5%). Greatest perceived benefits were convenient access to care and advice (n=88/219, 40.2%); regular contact with healthcare providers (n=54/219, 24.7%); and feelings of care, support or security (n=42/218, 19.2%).

5. DISCUSSION

5.1 Standardizing definitions and outcomes across studies

When reviewing the literature for both Study I, presentation to care with advanced HIV, and Study II, a gender comparison of HRQoL, comparison between previous studies was hindered by the lack of consistent definitions used for outcomes. Studies in sub-Saharan Africa on late presentation and presenting with advanced HIV have used definitions based on CD4 count, such as ≤ 100 cells/mm³ (40) or < 100 cells/mm³ (41); definitions based on categorization by clinical features, such as CDC B or CDC C (42), or WHO Stage 3 or 4 (43). Some researchers have used a combination of the two, for example WHO Stage 3 or 4 *or* a CD4 count less than 200 cells/mm³ (44). Of the eight studies included in the literature review for the study on advanced HIV at presentation to HIV care, no two studies used the same definition. A lack of common definitions of outcomes prevents direct comparisons between regions and time periods and makes it difficult to evaluate the impact of interventions designed to target presenting to care with advanced HIV. Although definitions of outcomes may at times been driven by resource constraints i.e. a lack of laboratory testing in poor settings, where it is not, it would be helpful to have standardized definitions in place.

This problem is not exclusive to sub-Saharan Africa, Antinori *et al* note that there have been more than 20 definitions of a “late presenter” used in the literature across Europe and elsewhere (45). They propose the following consensus definition of late presentation: persons presenting for care with a CD4 count < 350 cells/mm³ or with an AIDS-defining event, regardless of CD4 count. They define presentation with advanced HIV disease as presenting to care with a CD4 count < 200 cells/mm³ or presenting with an AIDS-defining event, regardless of CD4 count (45). Antinori *et al* suggest that if researchers prefer to use alternative definitions, that the consensus definitions are presented alongside their chosen ones. However, this may create problems associated with multiple outcomes, such as spurious conclusions. If researchers and others choose alternative definitions, data should be presented in such a way as to allow others to estimate the proportion of individuals presenting late to care and with advanced HIV. This would enhance comparability between studies and help to move the field forward.

5.2 The importance of measuring ‘retention in care’ versus ‘retention in clinic’ to estimate retention in HIV care

There have been numerous papers estimating retention in HIV care and many meta-analyses done. In sub-Saharan Africa alone, a systematic review published in 2011 included 28 studies from the region on retention in individuals for the time between testing positive for HIV and initiating treatment (14). For individuals on treatment, a systematic review by these same authors in 2007 included 33 studies (22). The studies included in these meta-analyses equated “retention in care” with “retention in clinic”; however, there is a large and important difference between the two. Geng *et al* highlighted this difference in their publication “Retention in care among HIV-infected patients in limited-resource settings: emerging insights and new directions” (18). Rather than viewing retention in care from a clinic-based perspective, i.e. an individual is considered retained if they come back to the clinic at which they were originally enrolled in HIV care, they considered retention in care from a patient-based perspective, in which a patient is considered to be retained in care regardless of whether they are active in care at the clinic at which they originally enrolled or active in HIV care at another clinic.

In Kibera, one of our study settings with an area of just 2.38 km², there were several other clinics that provided HIV care to where study participants may have switched their care. In addition, our study population was highly transient, so they might have also sought care in their village or hometowns, or in a new location entirely. The decentralization of HIV care in many sub-Saharan African countries has meant that individuals with HIV may have many options for HIV care. Estimating retention in care by using retention in clinic as a proxy measure may underestimate retention in care, as an individual who does not return to the clinic where surveillance or a study is being conducted may not necessarily be lost to care, but instead may be engaged in care at another clinic. Individuals may also transfer their care formally, or informally (‘silent transfers’), but unless these individuals are traced at the time point of interest, there is no way of knowing whether they are active in HIV care.

Both in our trial and cohort study, retention in care was substantially greater than retention in clinic. Among trial participants, retention in clinic was 65% (n=452/700), while retention in care was 80% (n=562/700) (46). When the cohort participants (n=75) were added to the trial population, 63% (n=486/775) were retained in clinic, while 79% (n=609/775) were retained in care (47). To quantify retention in care at 12 months, we actively traced, by telephone or in the community, every participant who did not return to the clinic at which they were originally enrolled to determine whether they were active in HIV care or not. In the cohort study, of 289 participants who required further investigation to determine their status, 43% (n=123) were found to be active in care at another clinic (47). This highlights how important participant tracing is to quantify retention in care, particularly in settings where there are multiple clinics at which individuals may seek their care, or when investigating retention in care among transient populations.

When I designed the cohort study to quantify retention in care, to the best of my knowledge, there was only one other study that estimated retention in care beyond retention in clinic. In this Ugandan study, a sampling-based approach was used to estimate retention in care using assumptions based on the vital status of those who did not return to the clinic (25). A tracker community traced a sample of 128 participants out of 829 who did not return to the clinic to estimate retention in care (25). Estimates of retention in care at 12 months in the Ugandan study were based on one of two scenarios: assuming all patients who were determined to be alive in the sample were retained in care and extrapolating this to estimate retention in care, which increased the estimate of retention in care to 90.9% from 82.3% who were retained in clinic; or alternatively, assuming all patients who were found alive were no longer in HIV care, which increased the estimate of retention in care to 85.8% from 82.3%. (These estimates included updated information from a short questionnaire on participants' care status administered at the time the tracker made contact with the participant.)

Since the Ugandan study, and while our study was underway, others have acknowledged the deficiencies of using retention in clinic as a proxy measure for retention in care, and they have conducted investigations to obtain more accurate estimates of retention. A large study in South Africa using National Health Laboratory Service data that involved 55,836 patients measured 6-year retention in clinic at 29%, whereas retention in care at 6 years was 63% (26). In a further study by Geng *et al* involving adults on ART in 14 clinics from Uganda, Tanzania and Kenya (21), retention in clinic at two years was 69%. After accounting for informal and formal transfers, the authors found that 83% were retained in care. Again, a substantial increase from retention estimates that only considered individuals who returned to their original clinic. Although it was thought that retention in clinic likely presented an underestimate of retention in HIV care, there was some thought that it may overestimate retention, as estimates typically come from larger, well-resourced clinics (26). These recent studies, together with ours, confirm that retention in clinic substantially overstates attrition, and underestimates retention in HIV care.

5.3 Mobile phone interventions to promote retention in HIV care

When this study began, there were no other studies that had been published examining whether text-messages could be used to promote retention in HIV care. While the WelTel Retain trial was underway, a trial in Mozambique using one-way text messages as appointment reminders concluded that they had no effect on retention in HIV care at 12 months (30). Using a shorter time frame, a before-and-after study in Swaziland found that one-way text messages did not improve the proportion of patients who returned to collect their CD4 results (31). Similarly, studies that have tested using text messages as appointment reminders outside of Africa have also failed to demonstrate effectiveness (32,33). In Africa, interactive text messaging and mobile phone calls have been successful in engaging mothers in care in PMTCT programmes (34,35). A study currently underway in Kenya that tests the same intervention (WelTel) examined in our study will provide further information on the effectiveness of mHealth interventions to retain mothers in PMTCT care (48).

Overall, based upon the available evidence, it appears that when text messages are used as appointment reminders, they fail to improve clinic attendance. Among PMTCT populations, patient engagement with text messages and mobile phone calls may be effective at retaining mothers in PMTCT programmes, at least in some sub-Saharan African settings. Our trial suggests that contrary to our hypothesis, two-way text messaging is not an effective intervention to improve retention in care during the first year of HIV care in a general HIV population, as we did not find an effect on Stage 1 care (patient returns to receive their CD4 test results), 6-month retention in clinic, or in retention in care at 12-months. There have been no other rigorous trials investigating mHealth interventions as tools to promote engagement in HIV care.

Our hypothesis was based on findings of a post-trial analysis of the WelTel Kenya1 data. WelTel Kenya1 investigated the effect of the intervention on adherence to ART at three clinics in Kenya (49). After the trial, we conducted an analysis of the data to determine factors associated with retention in clinic at twelve months (50). The odds ratio for the association between the intervention and attrition was 0.72 (95% CI 0.43-1.18, p-value 0.189) (50). Although the finding was not statistically significant, we believed the reduced odds of attrition among those who had received the intervention warranted further investigation in a separate trial.

The findings of the WelTel Retain trial should be taken into consideration the study's context. Retention in care at the clinics involved in the trial was unexpectedly high (81% in the control group). If the trial had been conducted at clinics where baseline retention in care was substantially lower, then room for improvement would have been greater, and the intervention may have been more likely to have an effect (if it served to mitigate barriers to coming to the clinic). In addition, the two clinics involved in the trial had clinical procedures in place to encourage retention, which would have increased retention in care among all patients and in both arms, regardless of the intervention. Individuals who missed a clinic appointment were called up to two times to reschedule the appointment. The intervention may have been more effective at clinics where there were no such measures in place. Finally, of the studies involving the intervention so far, the WelTel Retain trial had the highest proportion of non-response to messages sent (44%) (46). In the WelTel Kenya1 study, there was no response to 32% of messages sent (49). The clinics involved in the WelTel Retain trial were in extremely poor settings, in which participants cited reasons such as insufficient credit or a broken phone for not responding to the messages (46). It is possible that in a setting in which participants are able to more fully engage in the service, it may have been more likely to have been effective.

5.4 Trials with null findings

Publication bias towards studies with positive findings arises from both journals and scientists themselves. Editors may favour studies with positive results as they are cited more frequently, raising a journal's impact factor. Researchers may choose not to report their null findings for various reasons, including lack of priority and time; the perception that studies with negative or null findings are less likely to be accepted for publication; and having a personal or industry-sponsored stake in their findings (51). Together with

the publication of the WelTel Retain trial findings in *The Lancet Public Health*, Fox and Kaufman commented on the importance of publishing null findings (52), arguing that it is as important to know whether an intervention has an effect, as it is to know whether an intervention has no effect. This is particularly true for rigorously conducted, adequately powered studies that produce valid and precise findings.

The importance of having a published or publicly available study protocol with pre-determined outcomes cannot be understated. In a study with null findings, it prevents authors from data dredging or data HARKing (Hypothesizing After the Results are Known) (53). In this trial, and consistent with the CONSORT guidelines, the study team reported the trial outcomes in accordance with the published study protocol and ClinicalTrials.gov record. Any additional outcomes reported are highlighted in the published manuscript, together with the reason for reporting these outcomes. Any outcomes not listed in the protocol were decided upon before the data were analysed. During the manuscript review, the journal did an excellent job of ensuring that the outcomes reported were consistent with the published trial protocol (54) as well the CONSORT guidelines (55).

When the WelTel Retain trial started in 2013, ART eligibility was based on a CD4 count of 350 cells/mm³; therefore, there was a period of pre-ART care for many individuals. During pre-ART care, individuals were most at risk of attrition, compared to those on ART. We were particularly interested in seeing whether the intervention could improve retention during this critical period in the continuum of HIV care. Over the course of the trial, the CD4 threshold for treatment was increased to 500 cells/mm³, and in 2016, the WHO guidelines recommended a “treat-all” strategy, in which treatment should be offered to all persons who test positive for HIV regardless of CD4 their count (56). With the implementation of these new guidelines, the pre-ART period essentially vanished; however, retention in care, even among those who are on ART, remains an important issue that must be tackled to meet the UNAIDS 90-90-90 targets.

While the WelTel intervention was not found to be effective at promoting retention in care, a previous trial demonstrated that the service improved adherence to ART at 12 months. The findings from the two trials are not necessarily conflictual, despite null findings in one and positive findings in the other. If two groups are equally well retained in care, and one receives the intervention while the other does not, it is possible that they might have differing levels of adherence. So, while the findings from the WelTel Retain trial did not suggest an effect on retention in care in this setting, the intervention may still provide benefit to those with HIV in other ways, such as improved ART adherence and greater perceived support by patients from the clinic.

6. CONCLUSIONS

The WelTel Retain study, with its large sample size and comprehensive datasets, allowed for multiple investigations. The inclusion of those who were ineligible for the trial in a larger cohort allowed for more generalizable investigations than that which could have been conducted using a trial population alone. Studies included whether delayed diagnosis or delayed presentation to care after diagnosis may lead to presenting to care with advanced HIV; an analysis of gender differences in HRQoL at the time of diagnosis; and a quantification of ‘retention in care’ without having to rely on ‘retention in clinic’ as a proxy measure. The trial itself was the first rigorous study evaluating the effect of an interactive mHealth intervention on retention in care in an adult HIV population.

Using baseline data, we found that presentation to care with advanced HIV was primarily due to delayed diagnosis, rather than delayed linkage to care after diagnosis. In the second study, we found that men and women have similar self-perceived quality of life scores in mental health, with unemployment being associated with a clinically significant decrease in mental health in both genders. Women reported greater physical health, but the difference was not considered clinically important, and the factors related to physical health, such as a higher CD4 count, were similar for both genders. Both the cohort study focussing on retention in care and the trial demonstrated that in this setting, retention in clinic substantially underestimated retention in care. Although the WelTel intervention was well-received by participants, it did not improve retention during the first year of HIV care. New ways to improve retention in care for people living with HIV are required, particularly at the start of the cascade of HIV care.

7. RESEARCH AND POLICY IMPLICATIONS

Study I

Study I highlights the numerous definitions of ‘late presentation to care’ and ‘advanced HIV’ that have been used in the literature. To improve comparability across studies and over time, it is important that researchers use consistent definitions for these terms, which may be aided by the publication of consensus definitions for these terms (45). Even if researchers choose to use their own definitions, data should be presented in such a way as to allow others to estimate the proportion of individuals presenting late to care and with advanced HIV.

At the clinics involved in the study, presenting to care with advanced HIV appeared to be largely due to delayed diagnosis, rather than delays in seeking care after diagnosis. Variation by clinic suggests that outreach and other community-based efforts may drive earlier testing and linkage to care. Our findings highlight the ongoing importance of implementing strategies to encourage earlier HIV diagnosis, particularly among adults 30 years and older. To fulfil the new global HIV targets, efforts are needed to maximize earlier diagnosis and entry into care at the front end of the HIV care continuum. Otherwise, changing guidelines to recommend treatment earlier in the course of HIV infection will not achieve their intended outcomes.

Study II

This study was the first gendered analyses of HRQoL related to people with HIV in sub-Saharan Africa. As such, its findings need to be confirmed (or refuted) in further investigations. This study highlights the need for consistent use of validated instruments to measure HRQoL and rigorous studies that control for confounding. Given the strong association between unemployment and both mental and physical health, broader economic development in conjunction with HIV-specific workplace policies and programmes to prohibit discrimination in the workplace are required. Overall, differences between the genders in factors related to HRQoL, such as social support, should be considered in public health policy and interventions to improve HRQoL in those living with HIV.

Study III

Study III highlights the need for tracing studies and adequate tracing and attrition monitoring systems within routine HIV care to more accurately quantify retention in HIV care and reduce loss to follow-up from HIV programmes in sub-Saharan Africa. This study, together with the trial, demonstrate that ‘retention in clinic’ is a poor proxy for ‘retention in HIV care’. Methods that track patient care between clinics, including silent transfers, are required to more accurately estimate retention in care. Our findings are positive in that a greater proportion of people living with HIV were retained in care than was expected; however, our estimate of retention in care falls short of the level of retention required to fulfil the UNAIDS 90-90-90 targets. New interventions and

innovative health systems solutions are required to better retain people in HIV care as well as to bring back those clients who drop out of care.

Study IV

Throughout the course of the WelTel Retain trial, ART eligibility guidelines changed, bringing into question whether the millions of people now eligible for ART will have the same barriers to adherence and retention as under previous guidelines. To meet the UNAIDS HIV targets, these barriers must be investigated and addressed. The WHO suggested the use of text messaging to improve retention in HIV care, both specifically from enrolment in care to ART eligibility and for lifelong retention. This trial demonstrated that the WelTel service did not improve retention during the first year in HIV care, either from the time to diagnosis to ART eligibility or at 12-months. For this, new ways to improve retention in care in adult HIV populations are required, particularly at the start of the cascade of HIV care. In populations who are retained, evidence-based SMS interventions, including WelTel, could be used to improve adherence, which supports the second and third UNAIDS targets to have 90% of people who know their status on ART and 90% of those virally suppressed.

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10. APPENDIX

World Health Organization clinical staging of HIV/AIDS for Adults

Clinical stage 1

Asymptomatic

Persistent generalized lymphadenopathy (PGL)

Clinical stage 2

Moderate unexplained weight loss (10% of presumed or measured body weight)

Recurrent respiratory tract infections (RTIs, sinusitis, bronchitis, otitis media, pharyngitis)

Herpes zoster

Angular cheilitis

Recurrent oral ulcerations

Papular pruritic eruptions

Seborrhoeic dermatitis

Fungal nail infections of fingers

Clinical stage 3

Conditions where a presumptive diagnosis can be made on the basis of clinical signs or simple investigations

Severe weight loss (>10% of presumed or measured body weight)

Unexplained chronic diarrhoea for longer than one month

Unexplained persistent fever (intermittent or constant for longer than one month)

Oral candidiasis

Oral hairy leukoplakia

Pulmonary tuberculosis (TB) diagnosed in last two years

Severe presumed bacterial infections (e.g. pneumonia, empyema, pyomyositis, bone or joint infection, meningitis, bacteraemia)

Acute necrotizing ulcerative stomatitis, gingivitis or periodontitis

Conditions where confirmatory diagnostic testing is necessary

Unexplained anaemia (<8 g/dl), and or neutropenia (<500/mm³) and or thrombocytopenia (<50 000/ mm³) for more than one month

Clinical stage 4

Conditions where a presumptive diagnosis can be made on the basis of clinical signs or simple investigations

HIV wasting syndrome

Pneumocystis pneumonia

Recurrent severe or radiological bacterial pneumonia
Chronic herpes simplex infection (orolabial, genital or anorectal of more than one month's duration)
Oesophageal candidiasis
Extrapulmonary TB
Kaposi's sarcoma
Central nervous system (CNS) toxoplasmosis
HIV encephalopathy

Conditions where confirmatory diagnostic testing is necessary:

Extrapulmonary cryptococcosis including meningitis
Disseminated non-tuberculous mycobacteria infection
Progressive multifocal leukoencephalopathy (PML)
Candida of trachea, bronchi or lungs
Cryptosporidiosis
Isosporiasis
Visceral herpes simplex infection
Cytomegalovirus (CMV) infection (retinitis or of an organ other than liver, spleen or lymph nodes)
Any disseminated mycosis (e.g. histoplasmosis, coccidiomycosis, penicilliosis)
Recurrent non-typhoidal salmonella septicaemia
Lymphoma (cerebral or B cell non-Hodgkin)
Invasive cervical carcinoma
Visceral leishmaniasis

Reference: World Health Organization (WHO). Interim WHO clinical staging of HIV/AIDS and HIV/AIDS case definitions for surveillance [Internet]. 2005 [cited 2019 Apr 8]. Available from: <https://www.who.int/hiv/pub/guidelines/clinicalstaging.pdf?ua=1>